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PSYCHOLOGICAL AND PHARMACOLOGICAL FACTORS CONTROLLING GASTRO-INTESTINAL MOTILITY

Summary of Work from
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A. INTRODUCTION

The present contract supports a research program designed to study systematically the conditions which affect gastrointestinal motility and how the motility may be controlled. Early work in our laboratory (Davis, Garafolo, and Gault. J. comp. physiol. Psychol., 1957, 50, 519-523; Davis, Garafolo, and Kveim. J. comp. physiol. Psychol., 1959, 52, 466-475) reported an electrical recording method using external electrodes which could be used to record g.i. motility. Previous work on g.i. motility had been handicapped by the necessity of introducing some foreign object or substance, e.g., balloon or barium meal, into the stomach or intestinal tract, thus providing a source of stimulation which might, in itself, affect results obtained. Following standardization of the method, a research program was developed to study: the electrophysiological characteristics of g.i. motility, environmental and bodily conditions affecting g.i. motility, g.i. motility as a conditionable response, and effects of selected drugs on control of g.i. motility. Previous annual reports have summarized progress in all these areas; the details have been made available in published papers and technical reports.

B. RESEARCH COMPLETED

1. Gastrointestinal responses of "executive" and control subjects during a noise-avoidance task. This project was completed with the publication of a final report: Davis, R. C. and Berry, F. Gastrointestinal reactions during a noise avoidance task. Psychol. Reports, 1963, 12, 135-137. The project had involved the basic features of techniques used by Brady and his collaborators to produce peptic ulcers in monkeys, adapted for use with human subjects. Records of g.i. motility using external abdominal electrodes, were obtained from pairs of subjects "yoked" in a manner similar to Brady's "executive" and control monkeys. The executive member of each pair was presented with a task in which he could avoid an aversive noise stimulus programmed for every 30 seconds if he pressed a button during the five seconds just before the noise was due. The task was sufficiently difficult that the median number

of avoidances was 6.5 of a possible 20, no subject being successful on more than 12 trials. The control subject in each pair was unaware of the avoidance task and was equally exposed to whatever noise resulted from his partner's efforts. The "executive" subjects showed significant increases in gastrointestinal activity during the task period; while the control subjects showed no such changes.

2. Gastrointestinal reactions to response-contingent aversive stimulation. The obvious difference between the treatments of the yoked subjects in the research described in the preceding paragraph lies in the fact that the appearance of the aversive stimulus was "response-contingent" for the "executive" subjects and not for the controls: the former could avoid the stimulus by making an adequate response; the latter could not. Research designed to analyze in greater detail the g.i. reactions to response-contingent aversive stimulation has been completed; a summary of the study is being prepared to serve both as a technical report and as a manuscript for publication.

The research was designed: to study the effects of exposure to the standard noise-avoidance task over a longer period of time than did the Davis and Berry project; to analyze g.i. activity in terms of amplitude, displacement and peak response time; to examine separately the characteristics of g.i. activity during trials when the aversive stimulus was successfully avoided and when it was not; and, to permit a contingency analysis of g.i. activity under the four possible relations between successful and unsuccessful responses on successive pairs of trials. The main results may be summarized briefly as follows:

a. Throughout the entire task period amplitude of g.i. activity was significantly lower for trials on which avoidance was successful than for trials on which it was not.

b. Significant positive correlations between amplitude and unsuccessful responses and successive blocks of trials during the task period indicated a progressive rise in amplitude throughout the period. This is in contrast to the trend for amplitude on successful trials and during rest which showed no such increase.

c. During the task period peak response times were significantly shorter when avoidance responses were unsuccessful than when the aversive stimulus was avoided.

d. The contingency analysis showed that, when a "noise" trial followed an "avoidance" trial, a large and highly significant increase in amplitude occurred on the noise trial. When the two trials occurred in the reverse order, an equally large and significant decrease in amplitude for the avoidance trial was observed. A succession of like trials was not accompanied by any significant changes in amplitude.

Conditions involving response-contingent aversive stimulation where successful responses are limited by the difficulty of the task are frequently referred to as situations of "psychological stress." The study just described provides basic information about the characteristics of g.i. activity in one such situation, where the conditions have been standardized and can readily be reproduced. This knowledge may now be used in research designed to determine factors affecting these g.i. reactions to stress and to study means of controlling the reactions.

C. RESEARCH IN PROGRESS

1. Relations between stomach secretion and electrical recordings from the gastrointestinal system. In order to understand more fully the nature of g.i. motility measures, we had, at the time of our last annual report, begun work on a dog preparation in which, by surgical techniques, a stomach fistula could be created for measuring the rate of stomach secretion and for obtaining periodic samples for analysis. The preparation would also provide

means of attaching recording electrodes internally. The need for these studies arose from observations made during the last several years in examining records from surface electrodes attached to the abdomen of human subjects: a slow drift frequently appeared, which did not seem to be related to measures of g.i. motility. It was hypothesized that this slow drift could be associated with secretory potentials arising from the g.i. tract. Some attempts were made, using human subjects, to study this possible relationship by attempting to withdraw stomach fluids via a swallowed tube and by presenting stimuli presumed to produce secretion. The results were suggestive only and the experiments were discontinued because of difficulties arising from the stomach-tube technique. The dog preparation was devised as a more direct method for obtaining the data needed to test the basic hypothesis. Development has been completed on a preparation which functions satisfactorily over the period of several weeks needed for experimentation. During an intensive data collection phase, records were obtained for about 20 sessions, which included over 30 administrations of chemical stimulation, e.g. Histamine administered subcutaneously, selected to alter gastric secretion. Effects of the stimulation were monitored by continuous recording from three electrode positions for periods averaging close to one hour each, simultaneously with continuous collection of samples of secretion.

The slow waves in which we are interested appear as the so-called "displacement" measure in records obtained from external electrodes on the abdomen (Davis, Garafolo, and Kveim. J. comp. physiol. Psychol., 1959, 52, 466-475). Records from the dog preparation are first being subjected to this kind of analysis. Although the analysis is still in the process of being independently checked in accordance with our standard procedure, preliminary data have revealed a rather dramatic and consistent effect at the electrode referred to as "interral" in our study. This electrode was recording via the fluids from the inside of the stomach wall. Records from it appear to display

a large positive "on-effect" amounting to about 10 millivolts of positive change during a period of five minutes following Histamine injection when a large rise in secretion rate occurs. They also display a corresponding negative "off-effect" of similar magnitude coincident with the slower decline in secretion rates as the effects of the injection disappear. These responses were present in sufficient magnitude in most of our runs to leave no doubt of their existence. However, they did not appear in all cases and the interpretation of their origin(s) is as yet not completely clear. They do not quite fit our initial expectations with regard to relations with the slow waves of the external recordings; they may be of a similar type but exaggerated in form due to the strong means used to stimulate secretion and to the electrode location so favorable to picking up the activity of cells in the stomach wall, which presumably constitute the voltage-generating source.

Of greater potential experimental and clinical interest is the analysis of the records for relations between secretion and electrical potentials recorded from the electrode attached externally to the surface of the abdomen. Records from this electrode show slow wave activity which appears to be more in accordance with our initial expectations. During recording it appeared that predictions from these waves could be made about changes in the flow of stomach secretion occurring with a lag of about one minute. This impression is being subjected to quantitative test; preliminary analyses appear to give it support.

We plan to explore measures of the electrophysiological recordings other than the traditional measures of amplitude and displacement, which have shortcomings in the analysis of certain wave phenomena. Our measures of secretion were obtained at half-minute time intervals, which will be used in a point to point analysis of relations between secretion rates and electrical activity. We are also examining our data for possible relations between electrical activity and changes in the pH of secretion.

2. Gastrointestinal motility in animals with experimentally induced ulcers. Our plans for research during the period January to September 1962 included preliminary work on techniques for studying changes in g.i. motility accompanying experimentally induced ulcers. Observations by R. C. Davis and others have suggested that differential patterns of g.i. motility in normal subjects and in patients with ulcerous pathology may be recorded by the external electrode method. We wish to study the etiology of these differences by experimentally producing ulcers using monkeys as our primary subjects. During the period of the present report we have investigated several technical problems and have accumulated experience in working with several species of animals, including monkeys.

Our first explorations centered around the use of the squirrel monkey, Saimiri Scuirea, as subjects. This monkey is being used extensively in the department's laboratories for several types of behavioral and electrophysiological studies. It appeared to satisfy many of our research requirements: taming and handling presented no particular problems, nor did fitting the animals to the Brady-type restraining chairs we planned to use. We have successfully recorded, virtually without movement artifacts, from surface electrodes attached to the animals, even though they moved about considerably in their chairs. The animals learned the shock avoidance task, required by the Brady method of ulcer production, without particular difficulty, once they were adapted to the chair. However, problems did arise. We believe that more work is still needed on methods of attaching electrodes for recording over long periods of time. We have had major difficulties relating to the animals' general health: most animals supplied to us have developed serious respiratory or gastrointestinal ailments shortly after their arrival and particularly after being exposed to experimental procedures.

While working out solutions to these problems we have successfully undertaken preliminary work on external recording of g.i. motility from other animal species, e.g., rats and rabbits. Other researchers have described

experimental techniques for producing ulcers in these species. There would seem to be merit in a comparative approach to the general problem of studying relations between external recordings of g.i. motility and the tissue changes involved in the etiology of ulcerous conditions. The development of adequate techniques for such external recordings could also lead to useful means of studying ways e.g., the use of drugs, in which factors involved in the production of ulcers may be controlled.

3. Changes in gastrointestinal motility produced by variations in sensory input. Research on environmental conditions affecting g.i. motility has been continued, exploring certain leads arising from the study of effects produced by reduction in sensory input described in our last annual report. In that report we described small, though consistent, differences in g.i. motility under conditions in which visual and auditory stimulation were presented for the first five minutes of a 40-minute experimental session and were off during the final 35 minutes and conditions in which the two sources of stimulation were presented for the full 40 minutes. We pointed out that the "off" conditions were very similar to the normal sleep environment and did not contain the major feature of an ambiguous sensory input characteristic of several previous studies of "sensory deprivation", which suggest that effects of such conditions upon behavior may result from reduction in the "meaningfulness" of sensory input rather than from deprivation per se. The present extension of the study added a third set of conditions in which Ss wore translucent goggles to diffuse visual sensory input during the experimental session.

Eight additional males Ss were observed during two sessions. S lay on a cot in a well-lighted, sound-deadened room; he wore earphones over which could be presented a continuous white noise of low intensity. Recordings were made from surface electrodes attached to the upper left and upper right quadrants of the abdomen. During one 40-minute session four of the Ss were exposed to one of the conditions described above and four to the other. During the second session

the visual and auditory stimuli were presented for the first five minutes, after which the brightness of the light stimulus was increased in order to maintain the absolute level of visual stimulation, transluscent goggles placed over S's eyes and the auditory stimulus continued. The order of the two sessions was counterbalanced for the eight Ss.

By expanding the design in this way we have obtained data replicating the two conditions of the first phase of the study and have information regarding a third condition, which may contain a basic factor in generating the kinds of results associated with experiments on "sensory deprivation". The records have all been analyzed and are now being submitted to statistical treatment.

D. WORK PLANNED FOR JANUARY TO SEPTEMBER, 1963.

During the period from January to September 1963 we intend to concentrate out attention on two major research problems:

1. We will continue work on the project designed to study g.i. motility associated with experimentally-induced ulcers. This will require some additional pilot work on special recording techniques for animals. It will then proceed to studies of relations between external electrode recordings and conditions within the stomach, e.g., presence or absence of food, drug-induced changes in secretion, effects of drugs on motility. With this information as a background, we will be ready to undertake the final studies of changes in g.i. motility before, during and after the experimental induction of ulcerous pathology.

2. Continuing work with human subjects will concentrate upon studying effects of drugs on g.i. motility, using prototype agents which are claimed to affect various functions of the g.i. system.